REMARKS

Rejections under 35 U.S.C. §112

New matter

Pending claims 1, 3-5, 7-9 and 18 stand rejected under 35 U.S.C § 112, first paragraph for failure to provide a written description. Specifically, the Action states that the amendments submitted on November 1, 2004 constitute new matter because the components b) an amino acid, c) two linker functional groups and d) a spacer are not disclosed as separate components.

While not acceding to the grounds of the rejection asserted in the Office Action, Applicants have amended the claims in view of this ground of rejection. Specifically, Applicants have amended independent claim 1 to recite that the invention consists of a psychotropic, neurotropic or neurological drug, or an antibiotic, antibacterial, antimycotic, antiviral, antiproliferative or antineoplastic drug, an amino acid or derivative thereof that is 5-hydroxytryptophan, serotonin, or melatonin, and a spacer comprising two linker functional groups.

Applicants respectfully contend that there specification certainly discloses such embodiments. For example, the specification states:

> The present invention is directed to an improved method for delivering biologically-active compounds, particularly drugs including preferably antibacterial, antibiotic, antiviral, antimycotic, antiproliferative and antineoplastic drugs and agents, and neurotropic, psychotropic and anticonvulsant drugs and agents, to physiologically protected sites in an animal *in vivo*. This delivery system achieves specific delivery of such biologically-active compounds through *conjugating the compounds* with *an amino acid or amino acid derivative* that is specifically transported into said physiologically-protected sites. This invention has the specific advantage of facilitating the entry of such compounds into cells and tissues protected by such physiological barriers as the blood-brain barrier *via* an amino acid or amino acid derivative that is specifically transported into said physiologically-protected sites, achieving effective intracellular concentration of such compounds more efficiently and with more specificity than conventional delivery systems.
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> The invention provides compositions of matter comprising a biologically-active compound covalently linked to an amino acid or amino acid derivative that is specifically transported into a physiologically-protected site. Preferred embodiments also comprise a spacer molecule having two linker functional groups, wherein the spacer has a first end and a second

> end and wherein the amino acid or amino acid derivative is attached to the first end of the spacer through a first linker functional group and the biologically-active compound is attached to the second end of the spacer through a second linker functional group. In preferred embodiments, the biologically-active compound is a drug, most preferably an antibacterial, antibiotic, antiviral, antimycotic, antiproliferative or antineoplastic drug or agent, or a neurotropic, psychotropic or anticonvulsant drug or agent. Preferred amino acid or amino acid derivatives include but are not limited to hydroxytryptophan, serotonin, and most preferably melatonin. (Page 8, line 29 through page 9, line 23; *emphasis added.*)

Applicants respectfully contend that the claimed pharmaceutical compositions claim the combination of a drug (as disclosed in their specification and specifically enunciated in their amended claims) covalently linked to an amino acid or derivative thereof through a linker. The claims as amended do not introduce new matter; they merely recite the claimed pharmaceutical compositions by specifically reciting these three components of the compositions. Applicants respectfully contend that their amendments do not introduce new matter, and respectfully request that this ground of rejection be withdrawn.

Indefiniteness

Pending claims 1, 3-5, 7-9 and 18 stand rejected under 35 U.S.C. § 112, second paragraph for being indefinite for reciting "an amino acid or derivative thereof" because 5-hydroxytryptamine, serotonin and melatonin are not amino acids. Although not acceding to the correctness of the Examiner's position, Applicants have amended the claims to specifically recite the enumerated amino acid derivatives. Applicants respectfully contend that their amendments overcome the asserted ground of rejection, and respectfully request that this ground of rejection be withdrawn.

Moreover, the Action further asserts a rejection of the pending claims for reciting a "spacer;" Applicants note that this ground of rejection does not apply to claims 7-9 that do not contain this limitation. Applicants respectfully contend that the term is defined in their specification sufficiently for one of ordinary skill in the art to understand the meaning of the term. *See, for example*, the following explicit disclosure:

> For the purposes of this invention, the term "spacer" or "spacer moiety" is intended to encompass any chemical entity that links a biologically-active

compound and an amino acid or derivative thereof according to the invention. Such spacer moieties may be designed to promote or effect the delivery to or accumulation at specific organs, tissues or cells, or to promote, influence, modulate or regulate the release of the biologically-active compound at the desired target site. Such spacers may facilitate enzymatic release at specific organs, tissues and cell, preferably at extracellular sites therein; more preferably, said spacers inhibit enzymatic, hydrolytic or other release systemically in an animal. Spacer groups, as described herein, include, but are not limited to aminohexanoic acid, adipic acid, and other bifunctional organic acids; peptides including homopolymers such as polyglycine; substituted fatty acids; carbohydrate moieties including mono-, di- and other saccharides; oligonucleotides; polyamides, polyethylenes, and short functionalized polymers having a carbon backbone which is from one to about twelve carbon molecules in length. Particularly preferred embodiments of such spacer moieties comprise peptides of formula $(\text{amino acid})_n$, wherein n is an integer between 2 and 25 and the peptide is a polymer of one or more amino acids.

The term "linker functional group" is defined herein as any functional group for covalently binding the amino acid or derivative thereof or biologically-active agent to the spacer group. These groups can be designated either "weak" or "strong" based on the stability of the covalent bond that the linker functional group will form between the spacer and either the amino acid or derivative thereof or the biologically-active compound. The weak functionalities include, but are not limited to phosphoramide, phosphoester, carbonate, amide, carboxyl-phosphoryl anhydride, thioester and most preferably ester. The strong functionalities include, but are not limited to ether, thioether, amine, amide and most preferably ester. The use of a strong linker functional group between the spacer group and the biologically-active compound will tend to decrease the rate at which the compound will be released at the target site, whereas the use of a weak linker functional group between the spacer group and the compound may act to increase the release rate of the compound at the target site. Enzymatic release is, of course, also possible, but such enzyme-mediated modes of release will not necessarily be correlated with bond strength in such embodiments of the invention. Spacer moieties comprising enzyme active site recognition groups, such as spacer groups comprising peptides having proteolytic cleavage sites therein, are envisioned as being within the scope of the present invention. Specifically, such specifically-cleavable peptides are preferably prepared so as to be recognized by enzymes present in particular organs or tissues such as brain and other physiologically restricted or protected sites *in vivo*, so that the drug is preferentially liberated from the polar lipid conjugate at appropriate drug delivery sites. An illustrative example of such a specifically-cleavable peptide is a portion of the proopiomelanocortin family of peptides, which are cleaved in mammalian brain tissue to release a variety of peptides hormones and effector molecules, such as the

> enkephalins. Those of ordinary skill in the art will recognize other beneficial and advantageous specifically-cleavable peptides. The linker functional groups are selected to inhibit or prevent cleavage of the covalent linkage between the spacer and the biologically active compound, or between the spacer and the polar lipid carrier, at a site other than the specific site to which the conjugate is targeted.
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> The conjugates of the invention are preferably provided comprised of spacer moieties that impart differential release properties on the conjugates related to differential expression or activity of enzymatic activities in physiologically restricted or protected sites in comparison with such activities in systemic circulation or in inappropriate targets, such as hepatic, renal or hematopoietic tissues. Differential release is also provided in certain embodiments in specific cell types comprising such physiologically protected tissues. (page 19, line 7 through p. 20, l. 30)

Applicants respectfully contend that their explicit disclosure would apprise one of ordinary skill of the meaning of these claim terms, and that their disclosure traverses the asserted ground of rejection. Applicants respectfully request that the Examiner withdraw this ground of rejection.

Enablement

Pending claims 1, 3-5, 7-9 and 18 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. Specifically, the Action states that the specification does not enable the claims throughout their scope.

Applicants respectfully traverse this ground of rejection. The Action recognizes that related claims have been granted by the U.S. Patent and Trademark Office in U.S. Patent No. 5,149,794 ("Yatvin I"), U.S. Patent No. 5,543,389 ("Yatvin II"); and U.S. Patent No. 5,827,819 ("Yatvin III"). These patents establish that these specifications disclose the inventions claimed therein sufficiently to satisfy the requirements of 35 U.S.C. § 112, first paragraph. The claims are herein amended recite conjugates of drugs and amino acid derivatives; in contrast the claims of the Yatvin I, Yatvin II and Yatvin III patents recite conjugates of drugs, amino acids or peptides thereof and polar lipids. If the U.S. Patent and Trademark Office has determined that the disclosures of the Yatvin I, Yatvin II and Yatvin III patents satisfy the requirements of 35 U.S.C. § 112, first paragraph, *a fortiori* the instantly-claimed invention, which recites less complex drug conjugates is supported by the instant specification. Applicants thus respectfully contend

that the asserted ground of rejection is inconsistent with and contradictory to the determination of the U.S. Patent and Trademark Office regarding the disclosure required to support the scope of the pending claims, and respectfully ask the Examiner to withdrawn this ground of rejection.

Rejections under 35 U.S.C. §102(b)

Anticipation

Claims 1, 3-5, 7-9, and 18 stand rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,827,819 ("Yatvin III"). Applicants respectfully traverse-in-part and overcome-in-part this ground of rejection.

The basis for their traversal is that the Yatvin III patent does not disclose and every limitation in the claimed invention. Specifically, the Yatvin III patent does not disclose conjugates between 5-hydroxytryptophan, serotonin, or melatonin and any of the disclosed drugs as now claimed. Applicants thus respectfully contend that their claims as amended are not anticipated by the disclosure of the Yatvin III patent, and respectfully request that the Examiner withdraw this ground of rejection.

Rejections under 35 U.S.C. §103

Obviousness

Claims 1, 3-5, 7-9, and 18 stand rejected under 35 U.S.C §103 as being obvious over the disclosures of U.S. Patent No. 5,149,794 ("Yatvin I"), or U.S. Patent No. 5,543,389 ("Yatvin II"); taken in view of the disclosure of the Merck Index. Applicants respectfully traverse-in-part and overcome-in-part these grounds of rejection.

As discussed above with regard to the anticipation rejection set forth in the Office Action, neither the Yatvin I nor Yatvin II references teach, suggest or motivate the skill worker to produce pharmaceutical compositions that are conjugates between 5-hydroxytryptophan, serotonin, or melatonin and any of the disclosed drugs as now claimed. The Merck Index does not cure this deficiency. Thus, Applicants respectfully contend that there is no basis for asserting rejections based on 35 U.S.C. §103 contained in the Office Action against the claims as now presented. Applicants thus respectfully ask the Examiner to withdraw these grounds of rejection.

Obviousness-type double patenting rejection

Pending claims 1, 3-5, 7-9, and 18 stand rejected under the judicially created doctrine of obviousness-type double patenting over Yatvin I, Yatvin II, and Yatvin III.

For the reasons set forth in the arguments presented above concerning rejection under 35 U.S.C. §103, Applicants contend that the instant claims would not be obvious to one skilled in the art in light of the Yatvin patents. There is no teaching, suggestion or motivation to conjugate any of the drugs recited in the claims as herein amended to 5-hydroxytryptophan, serotonin, or melatonin. Like the statutory obviousness rejections, Applicants respectfully contend that none of the Yatvin patents support the asserted obviousness-type patenting rejection. Applicants thus respectfully ask the Examiner to withdraw these rejections.

CONCLUSION

Applicants respectfully request the reconsideration of this application, and earnestly solicit a favorable determination of patentability of all pending claims.

If the Examiner in charge of this application believes it to be helpful, Applicants invite the Examiner to contact their undersigned representative by telephone at (312) 913-0001 in order to expedite the prosecution of this application.

Respectfully submitted,
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